

## Review

# Contrast agents in angiocardiology

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Uncertainty still surrounds the mechanisms of severe idiosyncratic reactions to the intravascular radiological contrast agents. Hyperosmolality itself causes changes due to fluid shift from extravascular to intravascular compartments.<sup>1,2</sup> Contrast agents also exert direct actions on mechanical and electrophysiological cardiac function, which may be regarded as cardiotoxic. These may be detectable even during intravenous injection,<sup>3,4</sup> some 5% of normal individuals developing identifiable electrocardiographic changes during intravenous urography. They are clearly most important in cardiac investigations in which contrast is injected directly into cardiac chambers or coronary arteries, particularly since most patients undergoing such investigations have cardiac disease and may be particularly vulnerable to changes in cardiac rhythm and pump function.

Recently, new low osmolality contrast agents have become available.<sup>5</sup> By definition, these produce smaller osmolality mediated fluid shifts and fewer haemodynamic effects. Available data suggest that they may also possess lower intrinsic cardiotoxicity. We review what is known of the adverse cardiovascular effects of radiological contrast agents and consider the evidence that the new agents may be safer.

### Chemistry and pharmacology

Conventional intravascular radiological contrast agents are salts of triiodinated benzoic acid derivatives (Fig. 1a). The cation is either methylglucamine (meglumine) or sodium, or a mixture of both. Conventional materials in use differ only in respect of the balance of these cations and in the detailed structure of the substituted side chains  $R_1$  and  $R_2$ . In terms of general systemic toxicity, the various commercial compounds are clearly similar, although the precise cationic composition is important in cardiotoxicity (see below).

The need to obtain high contrast density in conve-

niently small volumes has resulted in commercial preparations with osmolalities between four and eight times that of plasma. Hyperosmolality is responsible, at least in part, for multiple adverse side effects including subjective sensations such as pain, flushing, nausea, and vomiting and objective effects such as vasodilatation and possible damage to vascular endothelium, erythrocytes, platelets, and basophils.<sup>5</sup> Intravascular administration of hyperosmolar compounds results in a major shift of fluid from extravascular to intravascular compartments. For example, intravenous injection of a dose of contrast material sufficient for an intravenous urogram causes the circulating volume to rise by 10–20%<sup>1,2</sup> within about one minute. As regards the patient with cardiac disease, therefore, hyperosmolality is undesirable partly because of the attendant volume overload but also because hyperosmolality determines much of the cardiotoxic effect of conventional contrast media.

Although it is accordingly important to appreciate that not all contrast adverse effects are entirely hyperosmolality related,<sup>6,7</sup> there is reason to consider lower osmolality agents desirable. Three such agents have been developed recently. Two of these are based on the principle that, since osmolality is proportional to the number of particles in solution and since conventional agents are salts which ionise into two parti-

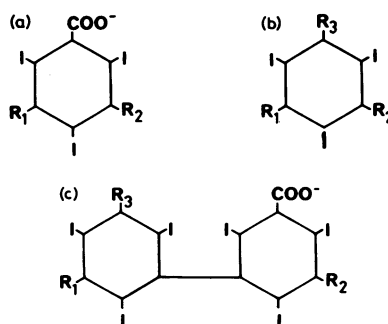


Fig. 1 The basic molecular structures of contrast agents (see text for details of (a), (b), and (c)).

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cles in solution, a similar non-ionic molecule with only one particle in solution will have approximately half the osmolality for a given iodine concentration. Such a compound is shown in Fig. 1b.  $R_3$  is a non-ionising side chain replacing the carboxyl group. This principle led to the production of the first low osmolality agent, Amipaque (metrizamide, Nyegaard Ltd), as long ago as 1974. This innovative compound had, however, several disadvantages. It was not heat stable, could not be sterilised by autoclaving, and was relatively unstable in solution. Consequently, it has to be presented as an expensive freeze dried lyophilised powder to be made up into solution using the solvent provided when required, which makes it expensive and inconvenient. Recently developed analogous compounds, Omnipaque (iohexol, Nyegaard) and Niopam (iopamidol; Bracco/Merck), have overcome the production, sterilisation, and stability problems of metrizamide. They are conveniently presented as solutions ready for immediate use and, although more expensive than conventional agents, are considerably cheaper than metrizamide.

An alternative approach has been to synthesise a larger molecule carrying twice the usual number of iodine atoms<sup>6</sup> so that for a given iodine concentration only half the number of molecules is needed. Consequently, even if prepared as a salt, ionising into two particles, it still offers the same improvement in the contrast to osmolality ratio as the non-ionic agents. Such a molecule is shown in Fig. 1c. The commercial version is Hexabrix (May & Baker), a mixture of sodium and meglumine salts of ioxaglic acid. This emphasises that the attributes of low osmolality and non-ionicity are not necessarily synonymous. Figure 2 shows the detailed structures of all these new compounds together with that of the conventional agent, sodium iothalamate (Conray 420, May & Baker).

In practice all three new compounds have achieved more than the theoretical 50% reduction in osmolality over their predecessors. Because of a tendency to aggregation of molecules in solution there is an overall reduction of approximately two thirds.<sup>5</sup>

#### Effects on blood volume and vasculature

As discussed in the last section, the introduction of hyperosmolar contrast agents into the peripheral venous or arterial circulation results in a substantial expansion of the plasma volume by 10–20%, for example, during a typical intravenous urogram. Blood pressure measurements recorded immediately after injection show a related rise in systolic and diastolic pressures. These effects are, as would be expected, less pronounced with the lower osmolality agents. The hypertensive response is short lived, being followed by hypotension due to generalised vasodilata-

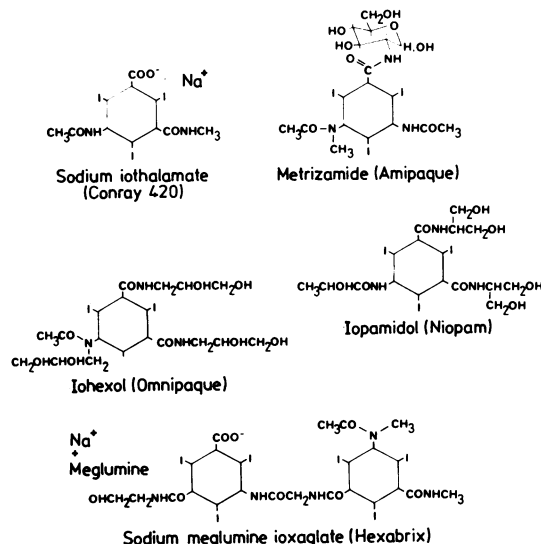


Fig. 2 The molecular structures of the new contrast agents.

tion. Hyperosmolality itself has been blamed for this vasodilatation, although other factors are probably involved, notably inhibition of acetylcholinesterase in blood and tissues.<sup>7</sup> In this respect and in their subjective effects all the new media produce appreciably smaller changes.<sup>7–9</sup>

Reduced systemic blood pressure prompts a reflex tachycardia. Changes in blood pressure and heart rate have major implications in patients with cardiac disease particularly of the coronary arteries (see below). In addition, the major hazards of systemic vasodilatation with intravascular contrast agents in patients with unresponsive cardiac outputs due to severe pulmonary hypertensive vascular disease may be minimised by using the low osmolality agents.<sup>10</sup>

#### Effects on the rheological properties of blood

Erythrocytes are deformed by contrast media by two mechanisms. Firstly, hyperosmolality causes a shift of water from within the erythrocyte to the surrounding plasma, producing a shrunken dextricocyte.<sup>11</sup> Secondly, even diluted iso-osmolar agents will produce a degree of deformity of a proportion of erythrocytes, the resulting cell having been termed an echinocyte.<sup>11</sup> Only the first mechanism, however, produces a rigidification of the erythrocytes<sup>12,13</sup> making them less able to deform to pass through the microcirculation, which, at its smallest (5  $\mu$ m), is smaller than the erythrocyte. This effect is important in right heart and pulmonary artery injections, in which rigidified red cells wedge in the pulmonary microcirculation producing an effective rise in pulmonary vascular resistance and a consequent rise in pulmonary artery pres-

sure.<sup>14</sup> This effect may also be important in contributing to the impairment of renal function that may be caused by contrast agents.<sup>15</sup>

### Effects on cardiac haemodynamics and coronary flow

Since 1962 the risks of selective coronary arteriography have been falling progressively,<sup>16,17</sup> mainly because of a growing appreciation of potential problems and of methods by which these may be avoided. Inevitably, however, the introduction of non-physiological solutions into the coronary arteries produces a series of behavioural alterations in the heart.

Selective coronary artery injection of conventional contrast agents initially causes slight but important depression of myocardial contractile function both in animals<sup>18</sup> and in man.<sup>19</sup> The effect is dosage dependent and most pronounced at the time of maximum coronary opacification. It persists longest in the ischaemic rather than the normally perfused heart.<sup>20</sup> The major consequence is a variable reduction in ventricular and arterial systolic pressure, a fall of 5–20 mm Hg being common, although more profound falls may occur.<sup>21</sup> This effect may be cumulative during repeated coronary contrast injections, emphasising the need to leave time for functional restoration between each. In the dog the severity of the depressant effects has been substantially reduced with the low osmolality agents when compared with conventional hyperosmolar agents,<sup>18,22</sup> and other comparative studies have shown differences in the magnitude of the depressant effects produced even by different commercial preparations of the conventional agents.<sup>23</sup> The part played by simple myocardial oxygen deprivation during coronary angiography appears to be unimportant.<sup>24</sup> Higgins suggests that calcium ion chelation by contrast materials or by their disodium edetate additives present as stabilisers and buffering agents may be important.<sup>18</sup> There is a close relation between cardiac exposure to calcium ions and cardiac contractile function.<sup>25</sup> The addition of ionised calcium to the contrast medium may reduce the depressant effect.<sup>26</sup> A study in which very low levels of calcium in venous blood leaving the coronary circulation via the coronary sinus were measured<sup>21</sup> during coronary contrast injections supports this argument. This work has emphasised the need to avoid slow flow and especially stasis of contrast media in the coronary circulation, a particular hazard in severely diseased arteries and in patients in whom coronary injection causes pronounced bradycardia. These considerations are clearly valid in patients undergoing percutaneous transluminal coronary angioplasty, in which context there may be a case (any considerations of adverse cardiac effects aside) for using the low osmolality

agents because of the desirability of minimising vascular endothelial damage.

Approximately 20 s after the coronary injection, enhancement of rebound contractile function is discernible<sup>18,27</sup> and may exceed control values particularly in animals.<sup>27</sup> This is attributable to a reflex increase in cardiac sympathetic drive together with release of myocardial catecholamines and histaminic substances and occurs despite peripheral vasodilatation. With coronary angiography peripheral systemic vasodilatation may partly be due to a vagal reflex mechanism associated with production of bradycardia and opposed by atropine.<sup>28</sup> The mechanism appears to be similar to that of the Bezold-Jarisch reflex, probably involving receptors in the left ventricular epicardium.<sup>29</sup> In patients cardiac output increases during this phase,<sup>23</sup> partly owing to an associated reduction in peripheral resistance. The phase of increased cardiac output may be lengthy, particularly when several coronary injections are given. Even with new agents the restoration of stable haemodynamics may take more than 10 minutes.<sup>30</sup> Enhanced contractile function may not always be salutary, particularly when critical myocardial ischaemia is present—for example, in unstable angina or during the course of coronary angioplasty—owing to possible deterioration in the ratio of regional myocardial oxygen supply to demand.<sup>31</sup>

Direct *in vitro* exposure of the working myocardium to contrast media results in reduced cardiac contractile function (a negative inotropic effect) as measured by various criteria.<sup>32,33</sup> It has usually been attributed to hyperosmolality of conventional contrast media and has been invoked to explain the early phase of depressed contractile function with coronary angiography. Recent studies suggest, however, that the constituents themselves as well as the osmolality may be important. Thus hyperosmolar sodium solutions exert negative inotropic actions on isolated papillary muscle, whereas hyperosmolar solutions of mannitol or dextrose may produce temporary positive inotropic effects.<sup>18</sup> The precise degree of hyperosmolality of the solution also influences the effects of contractility. Highly hyperosmolar solutions (over 500 mOsmol kg<sup>-1</sup>) exert progressively negative effects. In animals solutions of intermediate osmolality may actually cause enhanced contractile function<sup>18</sup> although this has been difficult to demonstrate in man.<sup>23</sup> The use of the intermediate osmolality range of newer contrast materials is therefore clearly important if the problems of early myocardial depression are to be avoided.

Although alterations in ventricular function during coronary arteriography are usually modest, major associated changes in coronary blood flow have been consistently reported. A triphasic sequence is discern-

ible.<sup>29,34</sup> During the immediate few seconds flow transiently falls, to be followed by a major hyperaemic response and then stabilisation. The initial flow reduction may reflect replacement of intracoronary blood by the more viscous contrast material. During hyperaemia flow frequently increases to more than twice the control value for 15–30 s, followed by a gradual return towards normal in 1–4 minutes. These results, from dog studies, have been reproduced in man,<sup>19,35</sup> although it has been difficult to detect any initial reduction in flow. Increased flow is principally the product of the hyperosmolality of the substance injected and may be brought about with, for example, intracoronary mannitol. Metrizamide (low osmolality) causes a smaller increase in coronary flow than diatrizoate.<sup>23</sup> Interestingly, the contrast washout time may, however, be faster with metrizamide, perhaps reflecting less red cell rigidification.<sup>22</sup> This results in venous phase films of better quality. The role of cholinesterase inhibition<sup>7</sup> in the response of the coronary circulation has not been evaluated. Adding calcium to metrizamide results in the same effects on blood flow as diatrizoate which shows that calcium ions again play a role. This effect is clearly an action on coronary resistance vessels and cannot be ascribed simply to altered coronary perfusion pressure<sup>19</sup>; the relative importance of dilatation of arteriolar smooth muscle and intracellular fluid removal from the vascular wall remains unclear.

The importance of increased coronary blood flow in the presence of coronary arterial disease in part depends on the site and extent of the coronary dilatation. If confined to relatively normal vessels flow may be diverted from territory served only by stenotic coronary arteries, generating a steal phenomenon, a problem which is analogous to that reported, for example, with other vasoactive materials such as isoprenaline and nitroprusside. If, however, dilatation also occurs in the stenotic coronary arterial system or in small collateral arterial channels feeding an ischaemic segment increased flow might be beneficial provided that it does not simply deliver an increased flow of contrast medium but is of sufficient duration to deliver whole blood after contrast clearance. Metabolic evidence of myocardial ischaemia at the time of increased coronary flow has been found in dogs<sup>36</sup>; the production of graded coronary stenosis progressively attenuates the hyperaemic response.<sup>37</sup> Parallel results have been achieved in patients by Holman and colleagues, using regional xenon washout measurements.<sup>38</sup> Thus increased flow is chiefly evident in normally perfused myocardium after coronary contrast injection, and stenotic arteries are less able to respond.

Left ventricular angiography using conventional contrast agents also initiates a triphasic series of

haemodynamic effects.<sup>39,40</sup> Cardiac contractility is initially enhanced in response to artificially increased ventricular volumes and in accordance with Starling's law. This is superseded within some 10 cardiac cycles by depressed ventricular function attributable to delivery of partially diluted but still appreciably hyperosmolar contrast to the working myocardium via the coronary arteries. At this time depressed contractile function combines with the onset of peripheral vasodilatation to cause pronounced reductions in systolic and diastolic arterial pressures. With contrast injections into the aortic root the initial phase of enhanced contractile function is likely to be absent, since the contribution to this phase made solely by afterload changes appears to be small<sup>39</sup> and contrast effects on the myocardium and periphery predominate.<sup>28</sup> The third phase, that of recovery of contractile function, emerges approximately one minute after left ventriculography, coinciding with maximum systemic vasodilatation and hypotension. In animals indices of ventricular contractility may exceed starting values at this time,<sup>39,40</sup> and stabilisation may take a full 15 minutes.<sup>40,41</sup> Mechanisms responsible for this rebound effect include reflex sympathetic stimulation, altered ventricular loading conditions, and possibly myocardial stimulation by diluted contrast material. In patients with coronary disease left ventricular ejection fraction may be slightly increased three minutes after ventriculography; simultaneously, diastolic compliance may be appreciably diminished and end diastolic pressure increased, possibly because of raised intramyocardial blood content.<sup>42</sup> Restoration time is principally determined by return to normal serum osmolality after ventriculography<sup>40,41</sup> and coronary arteriography.<sup>30,41</sup> Accordingly, low osmolality agents should provoke less profound haemodynamic effects.

Animal studies support this claim,<sup>27</sup> although initial investigations in man suggest that the total time course of changes with newer agents remains comparable, with effects persisting for some 10 minutes.<sup>30</sup> In terms of the reduced scale of haemodynamic effects, new contrast materials are demonstrably superior. When comparing conventional contrast with iohexol, Mancini and colleagues found substantially less hypotension and tachycardia with iohexol while achieving comparable coronary opacification despite slightly lower iodine content.<sup>43</sup> Cumberland found that Hexabrix was better tolerated than conventional materials in both adults and children with fewer episodes of tachycardia.<sup>10</sup> Experience suggests that nausea and vomiting in particular remain a problem with this agent. Gwilt and Nagle similarly found that iopamidol was less liable to reduce arterial pressure and increase heart rate,<sup>44</sup> although the subjective effects in their patients were not dissimilar to those

caused by standard contrast media.

### Effects on cardiac electrophysiology

The electrophysiological actions of contrast media are of major importance when injections are made into the coronary arteries, although effects are also apparent to a lesser degree when contrast is delivered into cardiac chambers or great vessels. They consist of a combination of direct and indirect neurally mediated changes in sinus rate, intracardiac conduction velocity, duration of the ventricular depolarisation—repolarisation process, and liability to tachyarrhythmias and bradyarrhythmias.

Sinus bradycardia follows within 2–10 s of either right or left coronary artery opacification in man, irrespective of coronary disease. The human sinus node artery derives from the right coronary artery in approximately 55% of cases and from the left circumflex in the remainder.<sup>45</sup> Sinus node depression may be caused by direct contrast infusion into the sinus node artery in dogs,<sup>46</sup> the depression correlating closely with the ionic strength of the material used. Even so, it is likely that the bradycardia induction during coronary angiography in patients is largely due to a reflex vagal mechanism, particularly in view of the consistency with which it occurs despite variable coronary anatomy.<sup>47</sup> The same considerations apply to altered atrioventricular conduction. The atrioventricular junction is in territory which receives heavy vagal innervation. The human atrioventricular node artery is usually a branch of the right coronary artery.<sup>48</sup> Selective atrioventricular node artery injection in dogs slows atrioventricular conduction as assessed simply by the PR interval.<sup>46</sup> The atrioventricular node appears to be the specific site of slowed conduction, on the basis of intracardiac recordings of the AH interval reflecting conduction from low atrial tissues through the atrioventricular node and into the proximal His bundle.<sup>49</sup> PR interval prolongation is detectable virtually equally in patients during right and left coronary angiography<sup>47</sup>; atropine blocks the effect,<sup>50</sup> and a vagal reflex is clearly involved. Below the atrioventricular node intraventricular conduction via the His bundle and bundle branch system is little affected. Conduction here is of course rapid and substantial percentage increments cause very little prolongation of the conduction time. The HV conduction interval representing conduction through this system is unchanged.<sup>51</sup> The duration of the QRS complex on the surface cardiogram is, however, slightly prolonged, implying slowing during more distal propagation of the depolarisation wavefront through the ventricular mass,<sup>52</sup> and bundle branch block patterns may appear temporarily.

The total time period occupied by the combined

processes of ventricular depolarisation and subsequent repolarisation is lengthened after administration of intracoronary contrast media. This is reflected in the lengthening of the electrocardiographic QT interval reported both in dog studies<sup>53</sup> and in man.<sup>54</sup> In patients opacification of the right coronary artery causes prolongation of the depolarisation—repolarisation process as accurately reflected by action potential duration registered by contact electrodes in the right ventricle,<sup>54</sup> whereas action potentials recorded simultaneously from the left ventricle are unaltered. The opposite situation is seen during left coronary injections. These sequences are accompanied by changed T wave morphology and QT interval prolongation. These effects may partly explain the increased liability to ventricular tachyarrhythmias, since regional inhomogeneity of repolarisation times throughout the ventricles is likely to favour their emergence, the situation possibly being similar to that seen in certain forms of congenital long QT syndrome.<sup>55</sup> Mancini and colleagues report that iohexol differs appreciably from conventional materials in leaving the QT interval unchanged.<sup>43</sup>

Electrocardiographic monitoring during coronary angiography shows increased amplitude and width of the QRS complex to the point of bundle branch block,<sup>56</sup> QRS axis deviation to the right in right coronary injections and to the left in left coronary injections, lengthening of the PR, PQ, and QT intervals, depression of the ST segment, and inversion of the T wave, the last to a greater extent in right than in left coronary injections.<sup>47, 53</sup>

Although animal data indicate generally reduced electrophysiological activity with newer agents,<sup>51, 57</sup> and studies in man support this concept,<sup>10, 43, 58</sup> rhythm disturbances remain a feature of left heart angiography with the new agents.<sup>44</sup>

The ventricular fibrillation threshold is reduced in relation to dose in animals after intracoronary injections of conventional contrast media; the effect lasts for about one minute.<sup>59</sup> Changes in cardiac cell membrane excitability are likely to be involved, together with effects on homogeneity of myocardial repolarisation velocity. The magnitude of the effect is diminished if calcium ions are added<sup>60</sup> and is less with the new agents.<sup>61</sup>

Table The viscosities of some contrast agents at different temperatures

| Contrast media | Viscosity (cP) |       |
|----------------|----------------|-------|
|                | 20 °C          | 37 °C |
| Urografin 370  | 18.5           | 8.9   |
| Omnipaque 350  | 23.3           | 10.6  |
| Niopam 370     | 18.5           | 8.6   |
| Hexabrix 320   | 15.7           | 7.5   |

The factors involved in producing these substantial electrophysiological changes include both hyperosmolality and chemical composition. Hyperosmolar dextrose can mimic the changes, and equiosmolar contrast agents have comparable effects, but diatrizoates have a greater effect than equiosmolar dextrose solutions. Faster rates of injection have the fewest electrophysiological effects.<sup>58</sup> In this context the viscosity of the contrast agents is of some importance. The Table summarises the data on the viscosities of some concentrations of new and representative conventional agents. The viscosities of the new agents are all appreciably higher than those of conventional agents. Viscosity is not only important as a limiting factor in achieving high injection rates but may contribute to stasis in the coronary microcirculation and contribute to myocardial ischaemia.

### The importance of cations

In terms of general systemic toxicity the cationic composition of an ionic contrast agent is of some importance. Thus the total sodium load delivered by large doses of sodium containing media may pose a threat to certain groups of patients: those with poor cardiac reserve, renal failure, or hepatic failure with ascites, and infants.<sup>62</sup> Meglumine salts, on the other hand, are thought to be associated with a higher incidence of bronchospasm<sup>63</sup> than sodium salts, a fact that may be explained by their greater tendency to stimulate histamine release from basophils and mast cells.<sup>64</sup>

The importance of cationic composition in cardiotoxicity was vividly illustrated when, as a result of the work of Gensini and di Giorgi, showing that high sodium concentrations were toxic to the myocardium while meglumine was protective,<sup>65</sup> the American manufacturers of Renografin 76 (sodium meglumine diatrizoate) reduced its sodium content virtually to zero without public announcement. As a direct result the incidence of ventricular fibrillation during cardiac procedures with this medium increased appreciably. Subsequent studies showed that the modified medium was capable of causing a pronounced prolongation of the depolarisation time. Although non-ionic agents are associated with low cardiotoxicity, ionic agents must clearly have the correct balance of cations. Too much sodium is indeed associated with high toxicity<sup>18</sup> but so is too little sodium; and whereas meglumine would appear to confer some protection against cardiotoxic effects this is no longer true if it is the only ion present. The only ionic low osmolality medium, sodium meglumine ioxaglate (Hexabrix), appears from its low cardiotoxicity to have achieved the correct cationic balance. The role of calcium is clearly also of great importance. The presence of the ionised

calcium in the contrast solution can reduce myocardial depression during coronary arteriography,<sup>18</sup> lessen the disturbance of electrical conduction, and oppose the consequent reduction in ventricular fibrillation threshold.<sup>57</sup> Calcium is partly chelated by disodium edetate present in contrast solutions as a buffering agent and partly bound by the anion in conventional ionic media.<sup>66</sup> Higgins *et al* have shown that conventional contrast materials summate with the calcium antagonist, verapamil, to depress the myocardium but did not encounter this potentially important undesired interaction using the non-ionic agent iohexol.<sup>67</sup>

### Anaphylactoid reactions

An appreciable proportion of the major adverse life threatening and fatal reactions which occasionally occur after contrast administration by any route are probably mediated by the haemodynamic and cardiotoxic effects discussed above. Many are, however, associated with allergy like clinical manifestations such as urticaria, bronchospasm, or laryngeal oedema, although the great weight of evidence is that they are not truly anaphylactic.<sup>68</sup> Recent thinking on their aetiology has centred on the activation of the coagulation, fibrinolytic, and kallikrein cascades by the contrast induced vascular endothelial damage. On the basis of such ideas the new contrast agents should be expected to be generally safer materials in all applications, since by virtue both of their lower osmolalities and their lower chemotoxicities they produce less endothelial damage.<sup>69</sup>

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